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10/534,325	09/12/2005	Jerome B Zeldis	9516-207-999	9771

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EXAMINER	
GEMBEH, SHIRLEY V	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/534,325	ZELDIS, JEROME B	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,7-9,11 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,7-9,11 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/14/06; May 18, 2006, May 5 2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 09/12/05, 05/18/06 and 7/14/06 has been received and acknowledged.

Response to Restriction

Applicant's election with traverse of claims 3-4, 7-9, 11 and 25. Applicant timely traversed the restriction (election) requirement in the reply filed. The traversal is on the ground(s) that it would not impose an undue burden. As shown by the following classifications, a majority of the combinations encompassed by the present claims has acquired a separate status in the art. For example, if there is a 6 membered ring containing one N it is classified in class 514 subclass 277 whereas if there is a 6 membered ring containing two Ns it is classified in class 514 subclass 247.

Notwithstanding that the classification of some of the active agents is co-extensive, all of the claimed compounds are patently distinct and fully capable of supporting separate patents. For the above reasons, an election of a single disclosed species for examination purposes is deemed necessary and proper. The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 3-4, 7-9, 11 and 25 are elected and are pending in this office action. Claims 1-2, 5-6, 10, 12-24 and 26-32 have been canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-4, 7-9, 11 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating or managing the inhibition of multiple myeloma, does not reasonably provide enablement for rheumatoid arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

1) Nature of the invention.

The nature of the invention is method of treating/managing or preventing a disease associated with undesired angiogenesis (very broad) administering a

therapeutically effective amount of the compound of claim 3 or the compound of claim 4 with a second active ingredient.

As stated, however, claims 3 and 4 recite a very large representation of diseases associated with undesired angiogenesis and the ability for one type of drug to treat/manage or prevent is very unpredictable.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease). No one particular drug even in view of the seemingly high level of skill in the art for a single drug cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-yl}carboxamide to treat a vast representation of angiogenesis let alone prevent. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between a representative number of that are encompassed by angiogenesis claimed as capable of being prevented by the above compound of the instant claim 3, one of skill in the art is unable

to reasonably predict possible results from the administration of the compound due to the unpredictability of the role of angiogenesis.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of skill in the art would first need to determine the type of angiogenesis disease to be prevented, and then determine which of the second active agent with the claimed drug would be suitable for said treatment and/or prevention.

4) Level of predictability in the art.

The art pertaining to the treatment of angiogenesis conditions remain highly unpredictable. As disclosed above, there is no absolute predictability even in view of the seemingly high level of skill in the art. Firstly, for a compound or genus to be effective against a disease associated with angiogenesis generally is contrary to medical science. Angiogenesis is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the reaction. There is no common mechanism by which arepresentative, or even most, angiogenesis arise. Accordingly, treatments for diseases associated with inflammation are normally tailored to the particular type of angiogenesis present.

5) Breadth of claims.

Claims 3 and 4 are extremely broad due to the vast number of possible diseases encompassed by the instant invention.

6) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be

individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which angiogenesis disease exhibits the desired pharmacological activity for the compound in claims 3 and 4 that would benefit from this activity of the compound.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the prevention of a representation of angiogenesis disease. As a result necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated by the compound of the instant claims in order to practice the claimed invention.

II. Claim 3-4, 8-9, 11 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that

applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" for the disease associated with undesired angiogenesis" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In other words, the Applicant has not described with sufficient clarity disease associated with undesired angiogenesis. This rejection can be overcome by Applicant including in claims 3 and 4 the limitation of claim 7.

Claim Rejections - 35 USC § 102

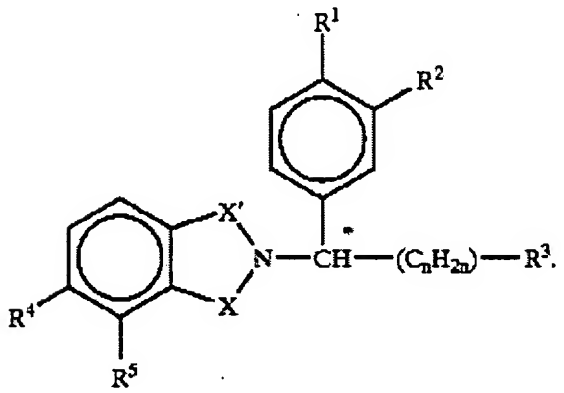
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

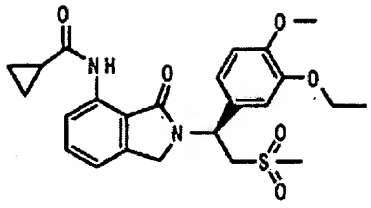
The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

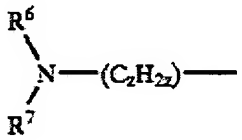
Claim 3-4, 7-8, 11 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Man et al. US 6,667,316 B1.

Man et al teach the current claim 3 a formula with the core structure



after substitution will result in the claimed

compound of instant claim 3  , to treat angiogenesis (see abstract) in its S isomer (see col. 11, lines 21-23) administered in an amount 1-1000 mg/day (see col. 12, lines 55-57) as in claim 25. With regards to claim 7 the compound is used to treat rheumatoid arthritis (see col. 13, lines 25-27).

To achieve the claimed structure R (4 or 5) (see col. 9 lines 64+, one of R4 or R5 is hydrogen and the other is  , where R7 is a cycloakyl having 3 carbons, (see col. 6 lines 53+) and R3 is SO_2 (see col. 6, lines 25+) that resulted in the claimed compound (see col. 38, lines 14+). The reference teaches that the compounds exist as substantially chirally pure isomers (see col. 13 lines 40+) as in claim 11. Though no specific isomer is given in the Man et al teaching, with regards to the compound in example 55, it is however anticipated that it is in the S isomer form since both forms can exist in chirally pure R and S isomer (see col. 11 lines 21+). The Man et al. also teach the drug can be used with other therapeutic agents (see col. 12 lines 40+) such as antibiotics as in the instant claims 4 and 8.

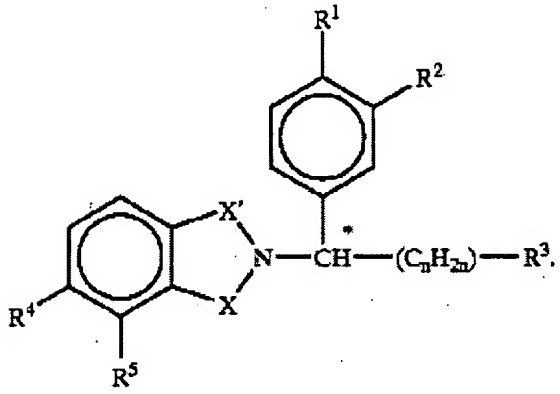
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

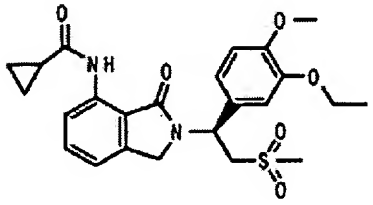
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-4, 7-9, 11 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Man et al. US 6,667,316 B1 in view of Hariri et al. US 2003/0235909

Man et al teach the current claim 3 a formula with the core structure

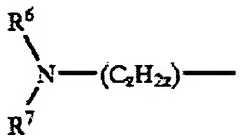


after substitution will result in the claimed compound of instant claim 3



, to treat angiogenesis (see abstract) in its S isomer (see col. 11, lines 21-23) administered in an amount 1-1000 mg/day (see col. 12, lines 55-57) as in claim 25. With regards to claim 7 the compound is used to treat rheumatoid arthritis (see col. 13, lines 25-27).

To achieve the claimed structure R (4 or 5) (see col. 9 lines 64+, one of R4 or R5



is hydrogen and the other is , where R7 is a cycloakyl having 3 carbons, (see col. 6 lines 53+) and R3 is SO_2 (see col. 6, lines 25+) that resulted in the claimed compound (see col. 38, lines 14+). The reference teaches that the compounds exist as substantially chirally pure isomers (see col. 13 lines 40+) as in claim 11. Though no specific isomer is given in the Man et al teaching, with regards to the compound in example 55, it is however readily envisage or obvious to the skilled artisan to isolate the form of preference.

The Man et al. also teach the drug can be used with other therapeutic agents (see col. 12 lines 40+) such as antibiotics as in the instant claims 4 and 8.

With the information provided and thus the claimed subject matter is not patentable distinct, since Man et al. teach the use of other active agents with the compound, it is within the purview of the skilled artisan to use other adjuvant drug therapy with the claimed compound. Adjuvant therapy is been used more frequently, for example Goodman and Steel suggest the use of other chemo drugs.

The instant invention differs only in citing the particular active agent used. One of ordinary skill in the art would have been motivated to employ the teachings of Man et al. with the suggestions by Goodman and Steele and used the appropriate active agent based on the malaise of the patient and expect a successful result in doing so.

Hariri et al. teach the use of amino-substituted isoindolines for the treatment of myelodysplasia (see page 268-269 and 271) using a compound that is in its isomeric form. Hariri et al. also teach the use of an additional active agent such as G-CSF (see para. 202-209) as in claims 9.

Although the Hariri et al. reference did not teach the same compound as that of the instantly claimed subject matter but teaches the active agent G-CSF is used in a combination therapy.

Therefore, one of ordinary skill in the art would substitute the active agent in the Man et al. reference with that of Hariri and expect a successful result in doing so.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **3-4, 7-9, 11 and 25** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **3,7,and 14** of U.S. Patent Application No. **10/515,270**. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to treating/preventing disease associated with undesired angiogenesis. The current application claims anticipate the copending application claims

As to the copending application claims 27 and 28 these claims refer to a product used. The products would have been used in the claimed method of treating in the instant application. Thus, the product of using is a set of precursor steps to the method of treating the undesired angiogenesis in the instant claims therefore are part of the obvious variation of the copending application claims compared to the current application claims.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
7/25/06

Ardin H. Marschel 8/3/06
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SUPERVISORY PATENT EXAMINER